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Mar 19 2007 07:18:03

1: J Biol Chem. 1996 Sep 6;271(36):21969-77.

Long-acting growth hormones produced by conjugation with polyethylene glycol.

Clark R, Olson K, Fuh G, Marian M, Mortensen D, Teshima G, Chang S, Chu H, Mukku V, Canova-Davis E, Somers T, Cronin M, Winkler M, Wells JA.

Department of Endocrine Research, Genentech, Inc., South San Francisco, California 94080, USA.

Derivatives of human growth hormone (hGH) of increasing size were produced by reaction with the N-hydroxysuccinimide ester of polyethylene glycol-5000 (PEG5000), a 5-kDa reagent that selectively conjugates to primary amines. By adjusting the reaction conditions and purification procedure, it was possible to isolate hGH derivatives containing up to seven PEG moieties that altered the Stokes radius and thereby the effective molecular masses of the unmodified hormone from 22 to 300 kDa. Fortunately, the most reactive amines were ones that did not lie in either of the two sites important for receptor binding. Nonetheless, increasing the level of PEG modification linearly reduced the affinity of hGH for its receptor and increased the EC50 in a cell-based assay up to 1500-fold. Most of the reduction in affinity was the result of slowing the association rate for the receptor. The clearance rate of hGH in rats was inversely proportional to effective molecular weight and closely fit a filtration model. We have tested the potency of these analogs by injecting them daily or every 6 days into hypophysectomized rats and determining the effects on body and organ growth. The efficacy of these analogs was optimal for hGH conjugated with 5 eq of PEG5000, and the potency was increased by about 10-fold compared with unmodified hGH. Such PEG-hGH derivatives show promise as long-acting alternatives to daily injections of hGH. More generally these studies show that improving hormone clearance properties, even at the expense of reducing receptor binding affinity, can lead to dramatic increases in hormone efficacy.

PMID: 8703002 [PubMed - indexed for MEDLINE]

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Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	43	530/399.ccls. and PEG SAME HGH	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:09
L2	224	PEG SAME HGH	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:09
L3	15	PEG SAME HGH and (TBI or traumatic or "brain injury" or subarachnoid or hemorrhage or haemorrhage)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:12
L4	3	PEG SAME HGH SAME (TBI or traumatic or "brain injury" or subarachnoid or hemorrhage or haemorrhage)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:10
L5	19	PEG.clm. SAME HGH.clm.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:12
L6	16	PEG SAME HGH.ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:15
L7	1	PEG SAME HGH.ab. and wang.in.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:15
L8	0	polyglycol SAME HGH.ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:15
L9	0	polyglycol SAME HGH	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:15

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L10	17	PEG SAME "human growth hormone".ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:21
L11	4	PEG SAME "human growth hormone".ab. and (TBI or traumatic or "brain injury" or subarachnoid or hemorrhage or haemorrhage)	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:16
L12	22	PEG SAME ("human growth hormone" or HGH).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:25
L13	32	PEG SAME ("human growth hormone" or HGH or GH).ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:25
L14	10	PEG SAME GH.ab.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:29
L15	0	PEG SAME "GH." and Carlsson.in.	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:29
S1	40	530/399.ccls. and PEG SAME HGH	US-PGPUB; USPAT; USOCR; EPO; JPO; DERWENT	OR	ON	2007/03/25 11:08